IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LTD. and SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE, Plaintiffs, v. LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants.	)	C.A. No.

COMPLAINT

Plaintiffs Glaxo Group Ltd. and SmithKline Beecham Corporation, d/b/a GlaxoSmithKline, for their Complaint against Defendants Lupin Ltd. and Lupin Pharmaceuticals, Inc., hereby allege as follows.

THE PARTIES

1. Plaintiff Glaxo Group Ltd. is a company organized and existing under the laws of England and having an office and place of business at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB60NN, United Kingdom.

2. Plaintiff SmithKline Beecham Corporation, d/b/a GlaxoSmithKline, is a Pennsylvania corporation having an office and place of business at 1 Franklin Plaza, Philadelphia, Pennsylvania 19102. Plaintiffs Glaxo Group Ltd. and SmithKline Beecham Corporation, d/b/a GlaxoSmithKline, are hereinafter referred to as "GSK."

3. On information and belief, Defendant Lupin Ltd. is a corporation organized and existing under the laws of India and having an office and place of business at Laxmi Towers, B Wing, Bandra Kurla Complex, Bandra (East), Mumbai, Maharashtra 400 051, India.

4. On information and belief, Defendant Lupin Ltd. manufactures numerous generic drugs, including, *inter alia*, cefprozil, lisinopril, and meloxicam, for sale and use throughout the United States, including in the State of Delaware.

5. On information and belief, Defendant Lupin Pharmaceuticals, Inc. is a Virginia corporation having an office and place of business at Harborplace Tower, 111 S. Calvert Street, 21st Floor, Baltimore, Maryland 21202.

6. On information and belief, Defendant Lupin Pharmaceuticals, Inc. is the United States agent for Lupin Ltd. for purposes including, but not limited to, making regulatory submissions to the United States Food and Drug Administration ("FDA").

7. On information and belief, Lupin Pharmaceuticals, Inc. also is the United States marketing and sales agent for Lupin Ltd. wherein, following FDA approval of an Abbreviated New Drug Application ("ANDA"), Lupin Ltd. manufactures and supplies the approved generic drug product to Lupin Pharmaceuticals, Inc., which then markets and sells the product throughout the United States, including in the State of Delaware.

8. On information and belief, and consistent with its practice with respect to other generic products, following any FDA approval of the ANDA at issue in this action, Lupin Ltd. will sell the generic product accused of infringement in this action through Lupin Pharmaceuticals, Inc. throughout the United States, including in the State of Delaware.

9. On information and belief, Lupin Pharmaceuticals, Inc. is a wholly owned subsidiary and alter ego of Lupin Ltd. On information and belief, for all purposes relevant to this action, Lupin Ltd. and Lupin Pharmaceuticals, Inc. are effectively the same entity and are referred to collectively hereinafter as "Lupin."

THE NATURE OF THE ACTION

10. This is a civil action for infringement of United States Patent No. 5,859,021 ("the '021 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. §§ 1 *et seq.*

JURISDICTION AND VENUE

11. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

12. This Court has personal jurisdiction over Lupin by virtue of the fact that, *inter alia*, Lupin has consented to personal jurisdiction in this Court for this action.

13. Venue is proper in this judicial district under 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT

14. On January 12, 1999, the '021 patent, titled "Antiviral Combinations," was duly and legally issued to Glaxo Group Ltd. as assignee. Since that time, Glaxo has been, and continues to be, the sole owner of the '021 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '021 patent is attached hereto as Exhibit A.

ACTS GIVING RISE TO THIS ACTION

15. The FDA granted approval of New Drug Application ("NDA") 20-857 to GSK in September 1997 to sell an oral tablet dosage form containing 150 mg of lamivudine and 300 mg of zidovudine for use in treating Human Immunodeficiency Virus ("HIV") infection in humans. The tablets approved under GSK's NDA are prescribed and sold in the United States under the tradename COMBIVIR®.

16. On information and belief, on or before July 16, 2008, Lupin submitted ANDA 90-246 to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)).

17. ANDA 90-246 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of a generic oral tablet dosage form containing 150 mg of lamivudine and 300 mg of zidovudine for use in treating HIV infection in humans ("the Generic Product"), prior to the expiration of the '021 patent.

18. ANDA 90-246 contains an allegation under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act that the claims of the '021 patent are either invalid, unenforceable and/or not infringed by the manufacture, use or sale of the Generic Product. GSK received written notification of ANDA 90-246 and its § 505(j)(2)(A)(vii)(IV) allegations on July 17, 2008.

19. On information and belief, and consistent with its practice with respect to other generic products, Lupin Ltd. has designated Lupin Pharmaceuticals, Inc. as its agent in the United States for purposes of filing ANDA 90-246 and for marketing and selling the Generic Product in the United States, including in the State of Delaware, upon any approval of ANDA 90-246.

20. Lupin Ltd.'s submission of ANDA 90-246 with its § 505(j)(2)(A)(vii)(IV) allegations to the FDA through its subsidiary and agent Lupin Pharmaceuticals, Inc. constitutes infringement of the '021 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Ltd. commercially makes, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States, or induces or contributes to any such conduct

during the term of the '021 patent, it would further infringe that patent under 35 U.S.C. § 271(a), (b) and/or (c).

21. Lupin Pharmaceuticals, Inc. is jointly and severally liable for the infringement of the '021 patent. On information and belief, Lupin Pharmaceuticals, Inc. actually filed ANDA 90-246 with the FDA and otherwise participated in, contributed to, aided, abetted and/or induced the submission of ANDA 90-246 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

22. Lupin Pharmaceuticals, Inc.'s filing of ANDA 90-246 and other participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 90-246 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitute infringement of the '021 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Pharmaceuticals, Inc. commercially manufactures, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States, or induces or contributes to any such conduct during the term of the '021 patent, it would further infringe the '021 patent under 35 U.S.C. § 271(a), (b) and/or (c).

23. Lupin had actual and constructive notice of the '021 patent prior to filing ANDA 90-246 and, on information and belief, was aware that the filing of ANDA 90-246 with its § 505(j)(2)(A)(vii)(IV) allegations with the FDA constituted an act of infringement of the '021 patent.

24. GSK will be irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. GSK does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Lupin has infringed the '021 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA 90-246 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration date of the '021 patent, including any extensions and additional periods of exclusivity;

C. That, pursuant to 35 U.S.C. § 271(e)(4)(B) and otherwise, Lupin, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from making, using, offering to sell or selling the Generic Product within the United States, or importing the Generic Product into the United States, prior to the expiration of the '021 patent, including any extensions and additional periods of exclusivity;

D. That GSK be awarded monetary relief if Lupin commercially makes, uses, offers to sell or sells the Generic Product within the United States, or imports the Generic Product into the United States, prior to the expiration of the '021 patent, including any extensions and additional periods of exclusivity, and that any such monetary relief be awarded to GSK with prejudgment interest; and

E. That GSK be awarded such other and further relief as this Court deems just and proper, including any appropriate relief under 35 U.S.C. § 285.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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August 29, 2008
2458334

EXHIBIT A

US005859021A

United States Patent [19]

Cameron et al.

[11] Patent Number: 5,859,021

[45] Date of Patent: *Jan. 12, 1999

[54] **ANTIVIRAL COMBINATIONS**

[75] Inventors: **Janet Mary Cameron**; **Nicholas Cammack**, both of Greenford, United Kingdom

[73] Assignee: **Glaxo Group Limited**, Greenford, United Kingdom

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,627,186.

[21] Appl. No.: **605,610**

[22] Filed: **Feb. 22, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 219,176, Mar. 28, 1994, Pat. No. 5,627,186, which is a continuation of Ser. No. 883,169, May 15, 1992, abandoned.

[30] **Foreign Application Priority Data**

May 16, 1991	[GB]	United Kingdom	9110624
Oct. 8, 1991	[GB]	United Kingdom	9121381
Nov. 6, 1991	[GB]	United Kingdom	9123581

[51] **Int. Cl.**[6] **A61K 31/505**; A61K 31/70

[52] **U.S. Cl.** **514/274**; 514/50

[58] **Field of Search** 514/50, 274

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,047,409	9/1991	Belleau et al.	514/274
5,059,592	10/1991	Yokota et al.	514/50
5,108,993	4/1992	De Simone	514/50
5,116,823	5/1992	Calabresi et al.	514/50
5,371,079	12/1994	Kukla et al.	514/220

FOREIGN PATENT DOCUMENTS

0 374 096 B1	6/1990	European Pat. Off. .
WO 89/09056	10/1989	WIPO .
WO 90/08550	8/1990	WIPO .
WO 90/11081	10/1990	WIPO .
WO 90/14830	12/1990	WIPO .

OTHER PUBLICATIONS

Martin et al., The Inhibitory Activity of a Peptide Derivative Against the Growth of Simian Immunodeficiency Virus in C8166 Cells, *Biochemical and Biophysical Research Communications*, vol. 176, No. 1, pp. 180–188, 1991.

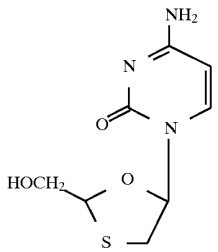
Speefor et al., 1989, Antimcirobial Agents & Chemothreapy vol. 33, pp. 920–923.

Primary Examiner—Russell Travers

Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

Combinations comprising a compound of formula (1)



(I)

or a pharmaceutically acceptable derivative thereof and an inhibitor of HIV replication, pharmacetical formulations thereof and their use in the treatment of HIV infections.

10 Claims, 4 Drawing Sheets

FIG. 1

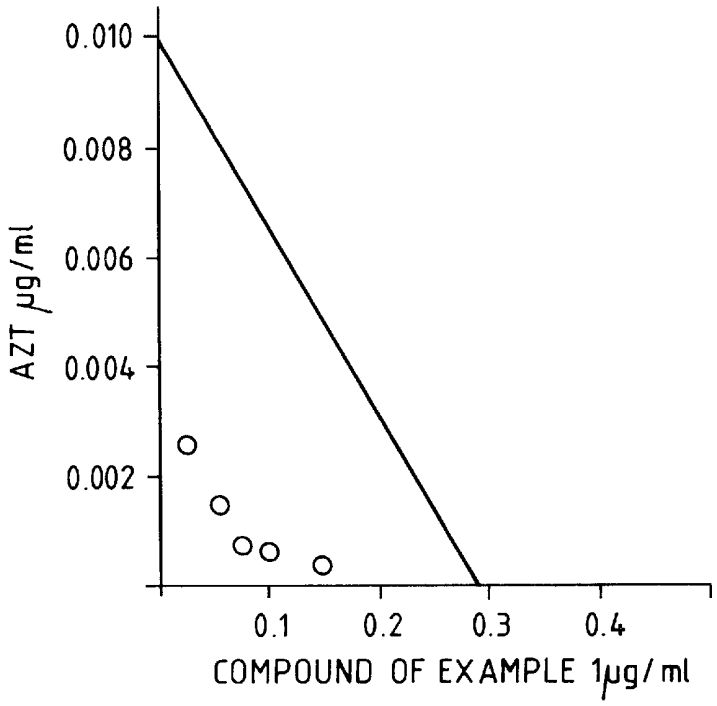

0.010
0.008
0.006
0.004
0.002
AZT µg/ml
0.1
0.2
0.3
0.4
COMPOUND OF EXAMPLE 1µg/ml

FIG. 2

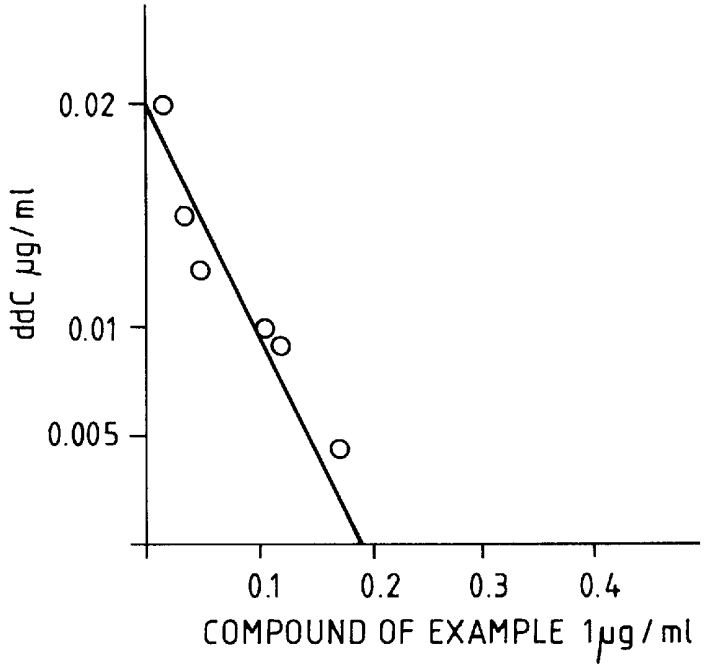

0.02
0.01
0.005
ddC µg/ml
0.1
0.2
0.3
0.4
COMPOUND OF EXAMPLE 1µg/ml

FIG. 3

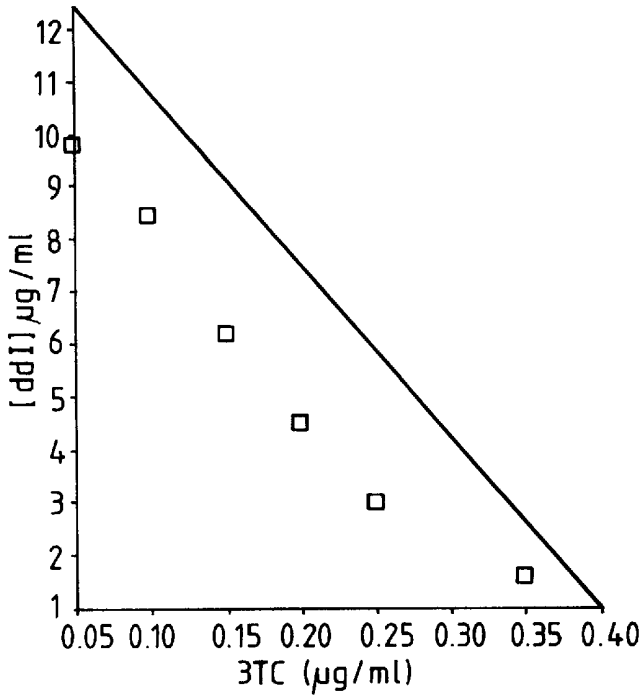

12
11
10
9
8
7
6
5
4
3
2
1
[ddI] µg/ml
0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40
3TC (µg/ml)

FIG. 4

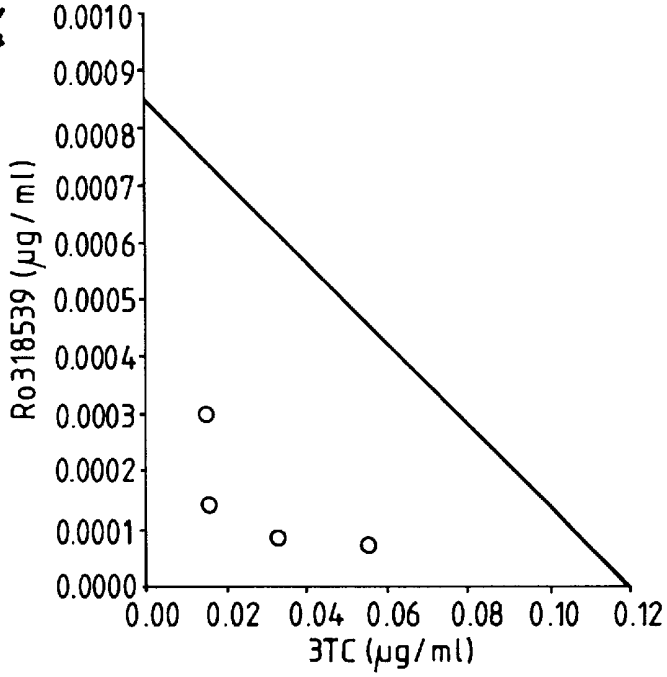

0.0010
0.0009
0.0008
0.0007
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0.0000
Ro318539 (µg/ml)
0.00 0.02 0.04 0.06 0.08 0.10 0.12
3TC (µg/ml)

FIG. 5

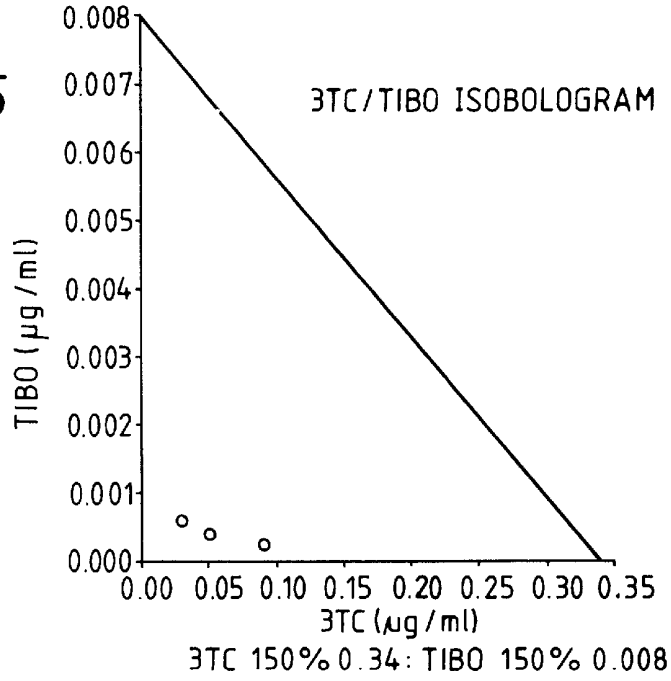

3TC/TIBO ISOBOLOGRAM
TIBO (μg/ml)
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35
3TC (μg/ml)
3TC 150% 0.34: TIBO 150% 0.008

FIG. 6

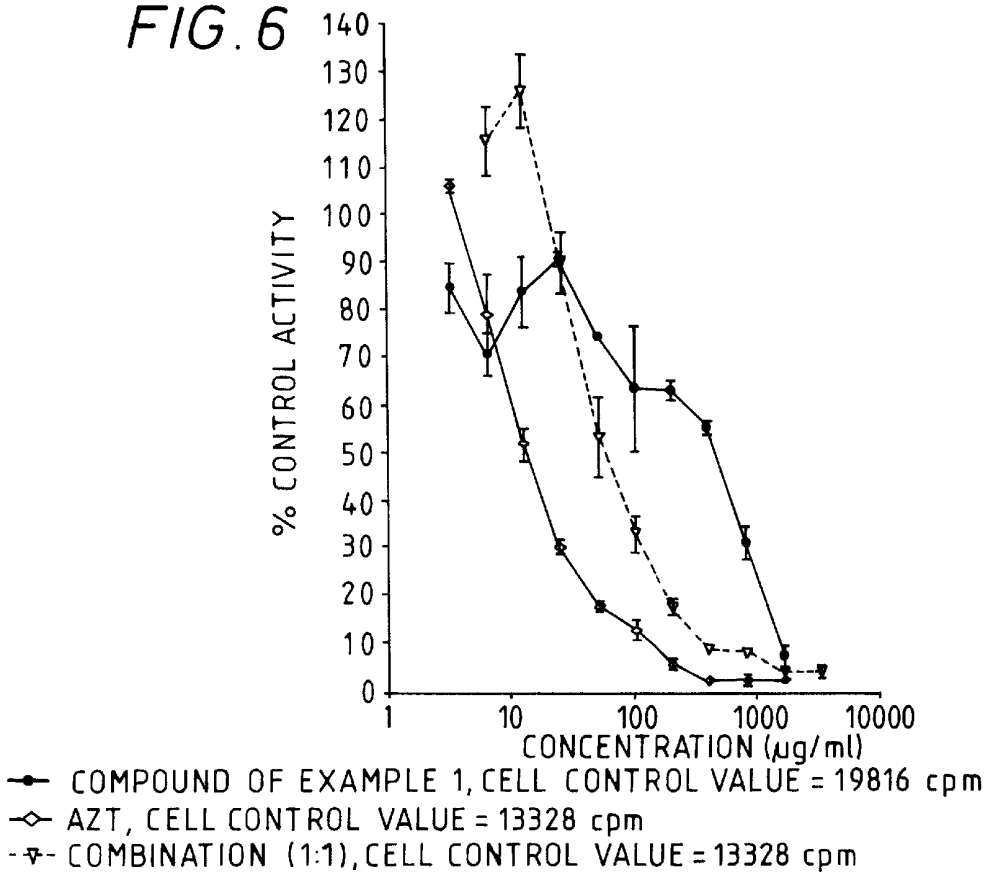
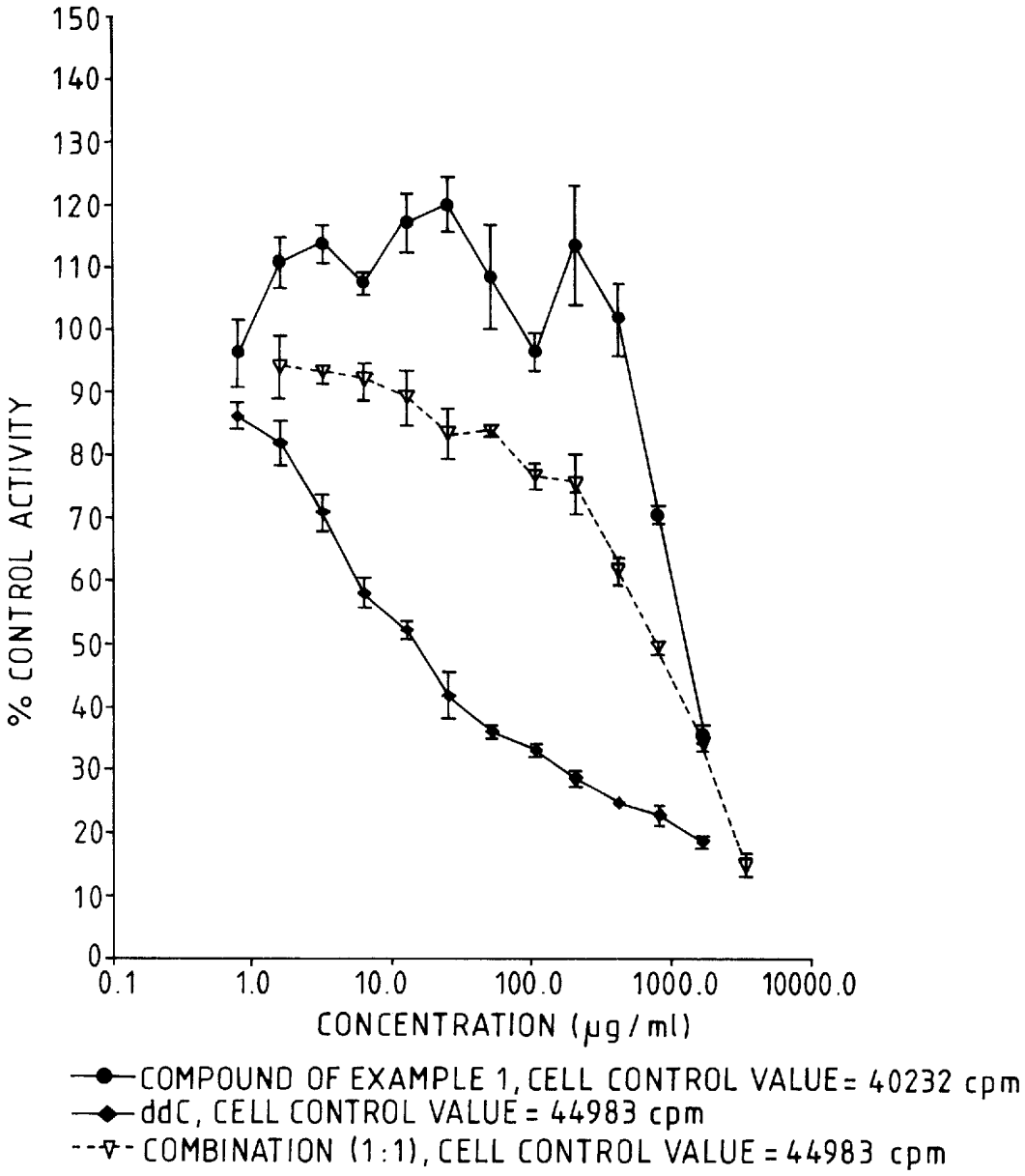

% CONTROL ACTIVITY
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
10000
CONCENTRATION (μg/ml)
COMPOUND OF EXAMPLE 1, CELL CONTROL VALUE = 19816 cpm
AZT, CELL CONTROL VALUE = 13328 cpm
COMBINATION (1:1), CELL CONTROL VALUE = 13328 cpm

FIG. 7


150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
% CONTROL ACTIVITY
0.1
1.0
10.0
100.0
1000.0
10000.0
CONCENTRATION (µg/ml)
COMPOUND OF EXAMPLE 1, CELL CONTROL VALUE = 40232 cpm
ddC, CELL CONTROL VALUE = 44983 cpm
COMBINATION (1:1), CELL CONTROL VALUE = 44983 cpm

ANTIVIRAL COMBINATIONS

This application is a Continuation of Ser. No. 08/219,176, filed Mar. 28, 1994; now U.S. Pat. No. 5,627,186 which is a Continuaton of Ser. No. 07/883,169, filed May 15, 1992, now abandoned.

The present invention relates to combinations of antiviral agents. More specifically it is concerned with combinations of 1,3-oxathiolane nucleoside analogues with other antiviral agents, in particular agents effective against HIV.

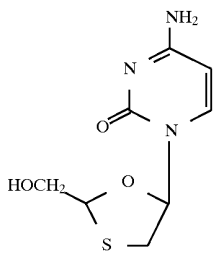
Human immunodeficiency virus (HIV) causes a variety of clinical conditions including the acquired immune deficiency syndrome (AIDS) and chronic neurological disorders. Nucleosides such as AZT, ddC and ddI inhibit HIV replication in vitro, and appear to exert their antiviral activity on the virus-encoded reverse transcriptase enzyme after metabolism by the cell to their 5'-triphosphate derivatives.

AZT reduces morbidity and mortality in patients with AIDS. However, HIV infection of cells results in integration of the virus genome into the host chromosome, and so it has been necessary to continue AZT treatment for long periods of time. The consequences of long-term AZT therapy are associated bone-marrow toxicity and the appearance of AZT-resistant variants of HIV-1. Similarly, some AIDS patients treated with ddC develop peripheral neurophathy and ddI has been shown to induce pancreatitis and peripheral neuropathy.

The use of combinations of compounds may give rise to an equivalent antiviral effect with reduced toxicity, or an increase in drug efficacy if synergy between compounds occurs. Lower overall drug doses will possibly also reduce the frequency of occurrence of drug-resistant variants of HIV. Many different methods have been used to examine the effects of combinations of compounds acting together in different assay systems. All of these methods have limitations and for example, some methods have been applied to systems other than those for which they were derived. AZT demonstrates synergistic antiviral activity in vitro in combination with agents that act at HIV-1 replicative steps other than reverse transcription, including recombinant soluble CD4 castanospermine and recombinant interferon alpha. However, it must be noted that combinations of compounds can give rise to increased cytotoxicity. AZT and recombinant interferon alpha have an increased cytotoxic effect on normal human bone marrow progenitor cells.

Combinations of AZT with other nucleosides have also been investigated. ddC eliminates the bone marrow cytotoxicity of high-dose AZT without affecting its antiviral activity. ddI and AZT show some enhanced selectivity in combination, through a synergistic antiviral effect acting over an additive toxicity to normal human bone marrow progenitor cells.

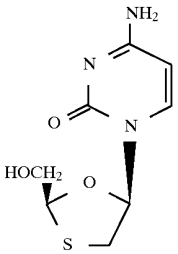
The compound of formula (I)



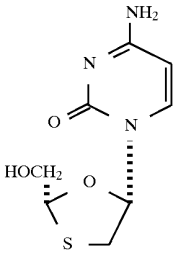
(I)

also known as BCH-189 or NGPB-21 has been described as having antiviral activity in particular against the human

immunodeficiency viruses (HIV's), the causative agents of AIDS (5th Anti-Aids Conference, Montreal, Canada 5th–9th Jun. 1989: Abstracts T.C.O.1 and M.C.P. 63; European Patent Application Publication No. 0382562). The compound of formula (I) is a racemic mixture of the two enantiomers of formulae (I-1) and (I-2):—



(I-2)



(I-1)

Although the enantiomers of the compound of formula (I) are equipotent against HIV one of the enantiomers (the(−) -enantiomer) has considerably lower cytotoxicity than the (+) enantiomer.

The (−) enantiomer has the chemical name (−)cis-4-Amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. It has the absolute stereochemistry of the compound of formula (I-1) which has the name (2R,cis))-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. This compound is now known as 3TC.

We have now found that the compound of formula (I) and, in particular its (−)-enantiomer exhibits unexpected advantages when used in combination with known inhibitors of HIV replication. In particular the compound of formula (I) shows a synergistic antiviral effect and/or a reduction in cytotoxicity when used in combination with known inhibitors of HIV replication.

There is thus provided in a first aspect of the invention a combination comprising the compound of formula (I) or a pharmaceutically acceptable derivative thereof and an inhibitor of HIV replication.

The inhibitor may comprise any inhibitor of HIV replication no matter its method of inhibiting HIV replication.. Such inhibitors include for example those which inhibit HIV reverse transcriptase, HIV protease and TAT and the like.

Such inhibitors include for example 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxyinosine (ddI), N'-[1(S)-benzyl-3-[4a(S), 8a(S)-3(S)-(tert-butylcarbamoyl)decahydroisoquinoline-2-yl]-2(R)-hydroxypropyl]-N"-(quinolin-2-ylcarbonyl)-L-asparaginamide (Ro 31-8959) and (+)-S-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)-imidazo(4,5,1-jk)(1,4)-benzodiazepin-2(1H)thione(R-82150; TIBO) or a pharmaceutically acceptable derivative thereof.

Preferably the compound of formula (I) is in the form of its (−) enantiomer (3TC).

Preferably the inhibitor of HIV replication is selected from AZT, ddI, Ro 31-8959 or R-82150(TIBO).

Particularly preferred as the inhibitor of HIV replication is ddI or, especially, AZT.

When the Compound formula (I) is in the form of the (−)-enantiomer it will normally be provided substantially free of the corresponding (+)-enantiomer, that is to say no more than about 5% w/w of the (+)- enantiomer, preferably no more than about 2%, in particular less than about 1% w/w will be present.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a parent compound or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) the parent compound or an antivirally active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compound of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof, at functional groups in both the base moiety and at the hydroxymethyl group of the oxathiolane ring. Modification at all such functional groups are included within the scope of the invention. However of particular interest are pharmaceutically acceptable derivatives obtained by modification of the 2-hydroxymethyl group of the oxathiolane ring.

Preferred esters of the compound of formula (I) include the compounds in which the hydrogen of the 2-hydroxymethyl group is replaced by an acyl function

in which the non-carbonyl moiety R of the ester is selected from hydrogen, straight or branched chain alkyl (e.g. methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g. methoxymethyl), aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxymethyl), aryl (e.g. phenyl optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g. methanesulphonyl); amino acid esters (e.g. L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters.

With regard to the above described esters, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

In particular the esters may be a C_{1-16}alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), C_{1-6}alkyl, C_{1-6}alkoxy, nitro or trifluoromethyl groups.

Pharmaceutically acceptable salts of the compound of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4+ (where R is C_{1-4}alkyl) salts.

The compound of formula (I) is either synergistic with the second component of the combination and/or removes the cytotoxic effects of the second component.

The advantageous effects of the compounds of formula (I) and the second antiviral agents are realised over a wide ratio for example 1:250 to 250:1 preferably 1:50 to 50:1, particularly about 1:10 to 10:1. Conveniently each compound will be employed in the combination in an amount at which it exhibits antiviral activity when used alone.

It is expected that the present combinations will be generally useful against viral infections or virus-associated tumours in humans, and the method of their use to inhibit viral infectivity or tumour growth in vitro or in vivo is also within the scope of the present invention.

Thus there is provided in a second aspect a method for the treatment of a viral infection in a mammal, including man, comprising co-administration of an antiviral compound of formula (I) and an inhibitor of HIV replication. Therapeutic methods comprising administration of a combination of a compound of formula (I) and more than one of the second antiviral agents, either together or in a plurality of paired combinations, is also within the scope of the invention.

It will be appreciated that the compound of formula (I) and the second antiviral agent may be administered either simultaneously, sequentially or in combination. If administration is sequential, the delay in administering the second of the active ingredients should not be such as to lose the benefit of the synergistic effect of the combination. Preferably administration will be simultaneous.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a combination of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 1 to about 750 mg/kg e.g. from about 10 to about 75-mg/kg of bodyweight per day, such as 3 to about 120 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day of each of the active ingredients of the combination.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The combination is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of each active ingredient per unit dosage form.

Ideally the combinations should be administered to achieve peak plasma concentrations of each of the active compound of form about 1 to about 75 mM, preferably about 2 to 50 mM, most preferably about 3 to about 30 mM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredients, optionally in saline, or orally administered as a bolus containing about 1 to about 100 mg of each active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of each active ingredient.

While it is possible that, for use in therapy, the active ingredients of the combination may be administered as the raw chemical it is preferable to present combinations as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof and inhibitor of HIV replication together with one or more pharmaceutically acceptable carriers therefor and, optionally, other

therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurised packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebuliser or a pressurised pack or other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compound of formula (I) may be obtained as described in European Patent Application Publication No. 0382562.

Its individual enantiomers may be obtained from its racemate by resolution by any method known in the art for the separation of racemates into their constituent enantiomers. In particular they may be obtained from the known racemate by chiral HPLC, by enzyme mediated enantioselective catabolism with a suitable enzyme such as cytidine deaminase or by selective enzymatic degradation of a suitable derivative using a 5'-nucleotide. Methods for the preparation of 3TC are described in International Patent Application Publication No. W091/17159.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** isobologram of 3TC with AZT

FIG. **2** isobologram of 3TC with ddC

FIG. **3** isobologram of 3TC with ddI

FIG. **4** isobologram of 3TC with Ro31-8959

FIG. **5** isobologram of 3TC with R-871501(TIBO)

FIG. **6** shows dose response cure for AZT vis 3TC

FIG. **7** shows dose response cure for ddC vis 3TC

The following examples illustrate the invention but are not intended as a limitation thereof.

INTERMEDIATE 1

5-Methoxy-1,3-oxathiolane-2-methanol, benzoate

A solution of zinc chloride (1.6 g) in hot methanol (15 ml) was added to a stirred solution of mercaptoacetaldehyde,

dimethyl acetal (34.2 g) and benzoyloxy acetaldehyde (48.3 g) in toluene (1300 ml) which was then heated to reflux under nitrogen for 50 min. The cooled mixture was concentrated, diluted with some toluene, then filtered through Kiesulguhr. The combined filtrates and toluene were washed with aqueous saturated sodium bicarbonate solution (×2) and brine, dried ($MgSO_4$) then evaporated to an oil which was subjected to column chromatography on silica (2 kg, Merck 9385) eluted with chloroform to give the title product as an oil (45.1 g) a mixture of anomers (ca 1:1); 1H NMR (DMSO-d_6) 3.1–3.3(4H), 3.42(6H), 4.4–4.6 (4H), 5.41(1H), 5.46 (1H), 5.54 (1H), 5.63 (1H), 7.46 (4H), 7.58 (2H), 8.07 (4H); γmax ($CHBr_3$)1717.6 cm^{-1}.

INTERMEDIATE 2

(±)-cis-1-(2-Benzoyloxymethyl-1,3-oxathiolan-5-yl) -(1 H)-pyrimidin-2-4dione

A mixture of finely ground uracil(9.62 g) hexamethyl disilazane (50 ml) and ammonium sulphate (30 mg) was heated at reflux under nitrogen until a clear solution was obtained. This was cooled and then evaporated to a colourless oil, which was dissolved, under nitrogen atmosphere, in acetonitrile (100 ml). The solution was added to a stirred ice cooled solution of 5-methoxy-1,3-oxathiolane-2-methanol, benzoate (intermediate 1) (19.43 g), in acetonitrile (600 ml) and trimethyl silyl trifluoromethanesulphonate (14.7 ml) was added. The ice bath was removed, and the solution was heated at reflux under nitrogen for 45 mins. After cooling and evaporation, the residue was purified by column chromatography over 1 kg of silica gel (Merck 9385) eluting with chloroform/methanol 9:1. Appropriate fractions were cooled and evaporated to afford a crude residue. This was fractionally crystallized from the minimum of hot methanol (c.1200 ml) to afford the title compound (6.32 g) as white crystals. 1H NMR(d^6DMSO) δ 11.36 (1H,bs). 7.50–8.00 (6H,m), 6.20 (1H,t), 5.46 (2H,m), 4,62 (2H, m), 3.48 (1H, m), 3.25 (1H, m).

INTERMEDIATE 3

(t±)-(cis)-4-Amino-1-(2-benzoyloxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one

Method (a)

A suspension of cytosine (20.705 g) and ammonium sulphate (few mgs) in hexamethyldisilazane (110 ml) was stirred and heated at reflux for 2½ h, under nitrogen. Solvent was removed by evaporation, and the residual solid was dissolved in dry acetonitrile (350 ml). This solution was transferred using flexible needle techniques into a stirred, ice-chilled solution of 5-methoxy-1,3-oxathiolane-2-methanol, benzoate (Intermediate I) (43.57 g) in acetonitrile (650 ml) under nitrogen. Trimethylsilyl trifluoromethanesulphonate (33 ml) was added, the solution was allowed to warm to ambient temperature (1½ h) then heated to reflux for an overnight period. The residue mixture was concentrated, diluted with saturated aqueous sodium bicarbonate solution (500 ml), then extracted with ethyl acetate (3×500 ml). The combined extracts were washed with water (2×250 ml) and brine (250 ml) dried ($MgSO_4$) then evaporated to a foam which was subjected to column chromatography on silica (600 g, merck 7734), eluted with ethyl acetate-methanol mixtures to give a mixture of anomers (ca 1:1 31.59 g). The mixture was crystallised from water (45 ml) and ethanol (9.0 ml) to give a solid (10.23 g) which was recrystallised from ethanol (120 ml) and water (30 ml) to give the title product as a white solid (9.26 g);λmax (MeOH) 229.4 mm ($E^{1\%}$ 610); 272.4 mm ($E^{1\%}$ 1 cm 1 cm 293); ^{1}H NMR (DMSO d6) δ 3.14 (1H), 3.50 (1H), 4.07 (2H), 5.52 (1H), 5.66 (1H), 6.28 (1H), 7.22 (2H), 7.56 (2H), 7.72 (2H), 8.10 (2H).

Method (b) Phosphorus oxychloride (7.0 ml) was added dropwise to a stirred, ice-cooled suspension of 1,2,4-triazole (11.65 g) in acetonitrile (120 ml) then, keeping the internal temperature below 15° C., triethylamine (22.7 ml) was added dropwise. After 10 min a solution of (±)-cis -1-(2-benzoyloxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2, 4-dione (Intermediate 2) (6.27 g) in acetonitrile (330 ml)was slowly added. Stirring was then continued at room temperature overnight. The mixture was cooled by means of an ice bath and triethylamine (30 ml) was slowly added followed by water (21 ml). The resultant solution was evaporated, and the residue was partitioned between saturated sodium bicarbonate solution (400 ml) and chloroform (3×200 ml). The combined chloroform extracts were dried and magnesium sulphate, filtered and evaporated to give a crude residue (9.7 g). The residue was dissolved in 1,4-dioxan (240 ml) and concentrated aqueous ammonia solution (s.g 0.880, 50 ml) was added. After 1½ h the solution was evaporated and the residue dissolved in methanol. This caused precipitation of a solid, which was filtered off. The mother liquors were purified by column chromatography over silica gel (Merck 9385, 600 g). Appropriate fractions were pooled and evaporated to give the title compound as a fawn solid (2.18 g), identical to that obtained by Method (a).

INTERMEDIATE 4

(±)-(cis)-4-Amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one

A suspension of (cis)-4-amino-1-(2-benzoyloxymethyl-1, 3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (Intermediate 3) (8.19 g) and Amberlite IRA-400 (OH) resin (8.24 g) in methanol (250 ml) was stirred and heated to reflux for 1¼ h. Solids were removed by filtration then washed with methanol. The combined filtrates were evaporated. The residue was triturated with ethyl acetate (80 ml). The resulting white solid was collected by filtration to give the title product (5.09 g), 1H NMR (DMSO-d_6) 3.04 (1H), 3.40 (1H), 3.73 (2H), 5.18 (1H), 5.29 (1H), 5.73 (1H), 6.21 (1H), 7.19 (2H), 7,81 (1H).

EXAMPLE 1

(−)-cis-4-Amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1 H) pyrimidin-2-one

(i) Three 50 ml flasks of nutrient broth (Oxoid Ltd) were inoculated with a loopful each of *Escherichia coli* (ATCC 23848) scraped from a Nutrient Agar plate. The flasks were incubated overnight at 37° C. with shaking at 250 rev/min and then each flask was used to innoculate 41 of CDD medium (glutamic acid, 3 g/l; $MgSO_4$, 0.2 g/l K_2SO_4, 2.5 g/l; NaCl, 2.3 g/l, $Na_2HPO_42H_2O$, 1.1 g/l, $NaH_2PO_22H_2O$ 0.6 g/l cytidine, 1.2 g/l) in a seven litre fermenter. The cultures were fermented at 750 rev/min, 37° C. with aeration at 41/min. After growth for 24 hrs the cells were collected by centrifugation (5000 g, 30 minutes) to yield 72 g wet weight. The cell pellet was resuspended in 300 ml of 20 mM Tris HCl buffer (pH 7.5) and disrupted by sonication (4×45 seconds). The cell debris was removed by centrifugation (30,000 g, 30 minutes) and the protein in the supernatant was precipitated by addition of ammonium sulphate to 75% saturation. The precipitate was collected by centrifugation (30,000 g. 30 minutes) and the pellet was resuspended in 25

ml of HEPES buffer (100 mM, pH 7.0) containing ammonium sulphate (75% saturation). Enzyme solution was prepared by centrifugation at 12,000 rpm for 30 mins. The supernatant was discarded and the pellet dissolved in Tris HCl buffer (pH 7.0; 100 mM) to the original volume.

(ii) Intermediate 4 (115 mg was dissolved in water (100 ml), and stirred. Enzyme solution (0.5 ml) was added, and the mixture was maintained at a constant pH by the continual addition of HCl (25 mM). The conversion was monitored by chiral HPLC, which showed that the (+) enantiomer of the substrate was preferentially deaminated. After 22 hr the (+) enantiomer of the substrate (RT 12.5 min) had been completely removed, and the solution was adjusted to pH 10.5 by the addition of conc. sodium hydroxide.

The solution produced above was eluted through a column of QAE Sephadex (A25; Pharmacia; 30×1.6 cm), pre-equilibrated to pH11. The column was washed with water (200 ml) and then with HCl (0.1M). Fractions (40 ml) were taken, and analysed by reversed phase HPLC. Fractions 5–13, containing the unreacted (−) enantiomer of the substrate, were combined and adjusted to pH 7.5 with HCl. Fraction 47, containing deaminated product, was adjusted to pH7.5 with dil. NaOH. Analysis by chiral HPLC showed that this material was a mixture, consisting of one enantiomer (RT 10.2 min) as the major component with the other enantiomer (RT 8.5 min) as a minor component (e.e ca 90%).

(iii) Stage (ii) above was repeated on a larger scale. The compound of Example 1 (363 mg) in 250 ml of water was incubated with enzyme solution (0.5 ml), prepared as in Stage (i). Further aliquots (0.5 ml) of enzyme were added after 18 and 47 hrs. The reaction mixture was stirred for 70 hr., then left standing for a further 64 hr. Analysis by chiral hplc indicated that the (+) enantiomer of the substrate had been completely deaminated, and the resulting solution was adjusted to pH10.5 with NaOH.

The solution above was loaded onto the same QAE column, and eluted as in stage (i). Fractions 2–6, containing a mixture of the residual substrate and deaminated product, were bulked. Fractions 7–13, containing the residual substrate ((−) enantiomer), were bulked and adjusted to pH7.5. Fractions 25–26, containing deaminated product, were bulked and neutralised

Fractions 2–6 above were re-eluted through the same QAE column. Fractions 3–11 from this second column contained unrected substrate ((−) enantiomer). Fraction 70 contained the deaminated product.

(iv) The resolved substrate fractions from stage (ii) and (iii) were combined and adjusted to pH7.5. This solution was eluted through a column of XAD-16 (40×2.4 cm), packed in water. The column was washed with water, and then eluted with acetone: water (1:4 v/v). Fractions containing the desired (−) enantiomer were bulked and freeze-dried to give a white powder (190 mg).

The HPLC methods used above were as follows:—

1. Reversed Phase analytical HPLC

Column	Capital Cartridge Spherisorb ODS-2 (5 uM) 150 × 4.6 mm
Eluant	Ammonium dihydrogen phosphate (50 mM) + 5% MeCN
Flow	1.5 ml/min
Detection	UV, 270 nm
Retention Times	BCH 189 5.5 min deaminated BCH-189 8.1 min

-continued

2. Chiral analytical HPLC

Column	Cyclobond I Acetyl 250 × 4.6 mm
Eluant	0.2% Triethylammonium acetate (pH 7.2)
Flow	1.0 ml/min
Detection	UV, 270 nm
Retention Times	BCH 189 11.0 and 12.5 min deaminated BCH-189 8.5 and 10.2 min (The bioconversion was followed by monitoring the loss of the peak at 12.5 min., and accumulated of product at 10.2 min).

EXAMPLE 2

3.1 Antiviral Activities Alone or in Combination

Compounds were first serially-diluted in 2-fold decrements in 96-well microtitre plates. Chequerboard titrations were prepared by mixing 25 ml aliquots from each compound dilution both alone or in combination (to a final volume of 50 ml in new 96-well microtitre plates). Aliquots of MT-4 cells (10^6 cells/ml) in RPMI 1640 growth medium were infected with HIV-1 strain RF at a moi of 2×10^{-3} infectious doses/cell. Virus was adsorbed at room temperature for 90 minutes, after which the cells were washed in RPMI 1640 growth medium to remove unadsorbed virus and resuspended at 10^6cells/ml in RPMI 1640 growth medium. 50 ml of infected cell suspension were inoculated into wells containing compound or growth medium only. 50 ml of mock-infected cell suspension were inoculated into wells not containing compound. The plates were then incubated for 7 days at 37° C. in 5% CO_2/air.

After incubation, 10 ml of 3-[4,5-dimethyl thiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) at 7.5 mg/ml were added to all wells and the plates incubated for a further 90 minutes at 37° C. 150 ml of 10% (v/v) Triton X-100 in isopropanol were then added and the cells resuspended. After 15 minutes at room temperature the plates were analysed in a Multiskan MC (Flow Laboratories, Irvine, UK) reader at 405 nm. Conversion of yellow MTT to its formazan derivative is maximum in the uninfected untreated cells, and absent in untreated infected cells.

Dose-response curves were plotted for each compound alone (IC50% values) and for reciprocal titrations of each compound at a fixed concentration of the second compound. Isobolograms of all compound combinations giving IC50% values were plotted.

FIGS. **1** through **5** are isobolograms of 3TC in combination with AZT, ddC, ddI, Ro 31-8959 and R-82150(TIBO) respectively. If the IC50% values of compound combination lies on a line joining the IC50% values of each compound on its own, then the two compounds act additively. If the combination IC50% lie to the left of the line, the compounds are acting synergistically.

Dose response curve for 3TC in combination with AZT, ddC, ddI, Ro 31-8959 and R-82150 (TIBO) are shown in FIGS. **1–5** respectively.

No toxic effects were observed when the antiviral activities of the combinations were determined.

EXAMPLE 3

Cytotoxicities of Compounds Alone and in Combination.

In these experiments the cytotoxicities of 3TC, AZT and ddC alone and in combination (at mg/ml ratios of 1:1, 1:5

and 5:1) were compared in uninfected peripheral blood lymphocytes and an established T-lymphocyte cell line.

Cytotoxicity was measured using a [^{3}H]-thymidine uptake assy. Typical dose-response curves obtained for each compound or a 1:1 combination in PBL cells are shown in FIGS. **6** and **7**.

We claim:

1. A combination of anti-HIV compounds which comprises a mixture of first and second compounds wherein said first compound is (2R,cis)-4-amino-1-(2-hydroxy-methyl-1, 3-oxathiolan-5-yl)-1 H-pyrimidin-2-one or a pharmaceutically acceptable salt, ester or salt of said ester of said first compound and said second compound is 3'-azido-3'-deoxythymidine or a pharmaceutically acceptable salt, ester or salt of said ester of said second compound with the proviso that said first and second compounds of said combination are present in a ratio wherein the ratio of said first compound to said second compound is from about 1:2 to about 1:1 by weight.

2. The combination of claim **1** which further comprises a pharmaceutically acceptable carrier for said first and second compounds.

3. The combination of claim **1** wherein said first compound is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxythiolan-5-yl)-1H-pyrimidin-2-one and said second compound is 3'-azido-3'-deoxythymidine.

4. A method for the treatment of a mammal, including man, suffering from or susceptible to infection by HIV which comprises administering a combination of anti-HIV drugs wherein said combination includes first and second compounds; said first compound being (2Rcis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-1 H-pyrimidin-2-one or a pharmaceutically acceptable salt, ester or salt of said ester of said first compound and said second compound being 3'-azido-3'-deoxythymidine or a pharmaceutically acceptable salt, ester or salt of said ester of said second compound wherein the first and second compounds are administered in a ratio of said first compound to said second compound which is from about 1:2 to about 1:1.

5. The method of claim **4** wherein said first and second compounds are administered sequentially.

6. The method of claim **4** wherein said first and second compounds are administered simultaneously.

7. The method of claim **4** wherein said first compound is (2R,cis-4-amino-1-(2-hydroxymethyl-1,3-oxythiolan-5-yl)-1H-pyrimidin-2-one and said second compound is 3'-azido-3'-deoxythymidine.

8. The combination of claim **2** which is in the form of a dosage unit.

9. The combination of claim **3** which further comprises a pharmaceutically acceptable carrier for said first and second compounds.

10. The combination of claim **9** which is in the form of a dosage unit.

* * * * *

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

Glaxo Group Ltd. and SmithKline Beecham Corporation d/b/a GlaxoSmithKline

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Jack B. Blumenfeld and Karen Jacobs Louden, Morris, Nichols, Arsht & Tunnell LLP, 1201 North Market Street, P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200

DEFENDANTS

Lupin Ltd. and Lupin Pharmaceuticals, Inc.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury

PERSONAL INJURY
- ❒ 362 Personal Injury - Med. Malpractice
- ❒ 365 Personal Injury - Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
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- ❒ 660 Occupational Safety/Health
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Mgmt. Relations
- ❒ 730 Labor/Mgmt.Reporting & Disclosure Act
- ❒ 740 Railway Labor Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
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- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 810 Selective Service
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 875 Customer Challenge 12 USC 3410
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 892 Economic Stabilization Act
- ❒ 893 Environmental Matters
- ❒ 894 Energy Allocation Act
- ❒ 895 Freedom of Information Act
- ❒ 900Appeal of Fee Determination Under Equal Access to Justice
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from another district (specify) ❒ 6 Multidistrict Litigation ❒ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
35 U.S.C. Section 271

Brief description of cause:
patent infringement

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ❒ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Joseph J. Farnan, Jr. DOCKET NUMBER 07-713 (JJF)

DATE 8/29/08

SIGNATURE OF ATTORNEY OF RECORD /s/ Karen Jacobs Louden (#2881)

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity**. Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.